development of a safe and effective vaccine against streptococcal infection, which continues to be a serious health threat.

The Pending Claims

Prior to entry of the above amendments, claims 1 through 17 are pending. Claims 1 to 5 are directed to vaccines; Claims 6 to 17 are directed to methods of vaccinating a mammal.

The Office Action

The title of the invention is objected to as not being descriptive.

The drawings are objected to under 37 C.F.R. § 1.84.

Claims 1-17 remain rejected under 35 U.S.C. § 112, first paragraph.

Claims 1-4 remain rejected under 35 U.S.C. § 102(b) or in the alternative under § 103 as anticipated by Bjorck *et al.*

Claims 1-4 and 6-17 remain rejected under 35 U.S.C. § 103 as unpatentable over Bjorck *et al.* in view of Kehoe and Fischetti *et al.*

Claims 1 and 2 are newly rejected under 35 U.S.C. § 112 ¶¶ 1 and 2 on the basis that the term "derivative thereof" is not defined.

Claims 1-4 are newly rejected under 35 U.S.C. § 102 (a/b) as being anticipated by Kapur *et al.* or Tai *et al.* or Hauser *et al.* or Gerlach *et al.* or Yonaha *et al.*

Claims 5-17 are newly rejected under 35 U.S.C. § 103 as being unpatentable over Gerlach *et al.* or Hauser *et al.*, in view of Kehoe *et al.* and Fischetti *et al.* and Abe *et al.* and Kapur *et al.*

Amendments

Applicants have amended the title as suggested by the Examiner on the cover page and in the abstract.

Claim 1 has been amended to recite that the vaccine contains an amount of cysteine proteins sufficient to confer immunity to Group A *Streptococci* infection, and to substitute

--group A *Streptococci*-- for *"Streptococcus pyogenes."* The amendment to claim 1 finds support in the specification at p. 4, lines 20-21.

Claim 2 has been amended to remove the phrase "or derivatives thereof." The amendment to claim 2 finds support at p. 4, lines 14-16.

The Applicants will submit corrected formal drawings at such time as the Examiner indicates that allowable subject matter is present.

The 35 U.S.C. § 112, First Paragraph Rejection

The specification is objected to and claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to provide an enabling disclosure.

(1) The objection to the specification and the rejection of claims 1-17 under 35 U.S.C. § 112, first paragraph, is maintained.

Applicant contends that the "disclosure that streptococcal cysteine protease has activity as a vaccine against streptococcal infection satisfies the requirements of 112 1st paragraph," i.e.. "how to use" and cites In re Bundy. The fact pattern of In re Bundy was different from the instant application, as it was concerned with utility of analogs of known compounds. In the instant case, Applicant claims cysteine protease, exotoxin B, which cannot be considered "analogous" to M protein or any other antigen expressed by group A streptococci.

The first ground of the rejection is that the specification allegedly does not adequately teach how to practice the invention. In maintaining this ground of rejection, the Examiner dismisses out of hand the statements of Dr. Musser, who is an expert in the field of the invention. This is contrary to well established law. According to the PTO Examination Guidelines on Utility Requirement, an Examiner "must treat as true a statement of fact made by an applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement." (60 C.F.R. 36263).

Dr. Musser stated in his Rule 132 Declaration that, in determining appropriate dosage amounts and inoculation regimes for the cysteine protease vaccine, "the clinician . . . has the benefit of past experience using a different streptococcal protease, the M protein, as a human vaccine" (Musser Decl., ¶ 10). In response to this assertion, the Examiner states that the

claimed cysteine protease "cannot be considered 'analogous' to M protein or any other antigen expressed by group A streptococci" (Office Action, p. 2). However, the Examiner provides no evidence or reasoning in support of this assertion. The Examiner must therefore accept as true Dr. Musser's assertion that "the clinician can determine the appropriate dosage amount and inoculation regime by following well-established guidelines for peptide vaccines" and that the significant amount of experience using the M protein is useful as a guide or provide an affidavit stating the facts upon which she bases her opinion to the contrary. 37 C.F.R. § 107(b).

Further, Applicants disclosure contains "prophetic" examples of animals "vaccinated" with the cysteine protease which does not enable "activity as a vaccine" against streptococcal infection.

Applicant also points to Examples 15, pages 28-29, as documenting "how to use the invention." Example 15 is directed to the preparation of murine monoclonal antibody. The ability of an antigen when used to generate monoclonal antibody, is not indicative that it also has protective abilities. Example 16 is directed to measurement of antibody levels by ELISA. Example 18 is a paper protocol suggesting that animals were vaccinated intranasally (using the animal model of Bessen et al) and s.c. (using an animal model of Bunce et al). These paper examples are not considered enabling of vaccine claims to prevent streptococcal infections.

Although "examples" of dosages for the animal tests are given in the specification, these examples are also prophetic teaching only s.c. "vaccination. It not clear if one of skill in the art would extrapolate from "paper protocols" to similar dosages and routes of administration in humans.

Applicant has further submitted a 1.132 Declaration by Dr. Musser to traverse this aspect of the rejection.

The declaration of Dr. Musser is unsigned, however, if the declaration were properly executed, it is not sufficient to enable the claims as drafted.

The Declaration does not follow the methodology set forth in the specification, but teaches s.c. inoculation followed by i.p. This method is not contemplated by the specification.

Further, there are no attached articles or Exhibits 1-3, as referenced in the Declaration. Also, Applicant indicates that copies of Beachey et al, J. Exp. Med. D'Alessandri et al and Polly et al; Agarwal Lancet are "references of record." The previously filed IDS does not include these references.

The Examiner notes that the declaration of Dr. Musser is unsigned. Applicants submitted a signed copy of the declaration on April 17, 1995. However, it was not received in the PTO until April 21, 1995, which is after the instant Office Action was mailed. For the Examiner's convenience, Applicants submit herewith as Exhibit 1 a copy of the executed Declaration and attached Exhibits. Also attached as Exhibits 2-3, respectively, are copies of D'Alessandri *et al.* (1978) *S. Infect. Dis.* 138: 712-718 and Polly *et al.* (1975) *J. Infect. Dis.* 131: 217-224. The Beachey *et al.* reference is attached to Dr. Musser's Declaration.

The protocol set forth in the declaration is not the same as that disclosed, nor is the animal model the same as suggested in the specification. (See prophetic Examples 21-25.) Dr. Musser only indicates that protocols were "similar" to those taught. The specification suggests that an "intranasal immunization model of Bessen et al" is used to evaluate the effect of cysteine protease immunization on mucosal colonization or a "mouse cutaneous infection model of Bunce et al," is used against a "subcutaneous bacterial challenge." In the cutaneous infection model "abscess volumes and area of dermonecrosis is calculated and lesion size curves determined. (See page 30.) Neither of these animal models is used in the declaration.

Further, the animal model does not typify or correlate to any "infection" caused by S. pyogenes.

The claims recite streptococcal infection selected from a group of pharyngitis, tonsillitis, skin infections, acute rheumatic fever, scarlet fever, post-streptococcal glomerulonephritis and toxic-shock-like syndrome. Other claims require vaccination of humans with a vaccine comprised of the cysteine protease and an M antigen.

Bunce et al indicate that animal models which do not "closely simulate humans cutaneous infections" are "more like animal test systems." Bunce et al indicate that this [animal] model (cited in the specification) is "a potentially relevant animal model for nosocomial cutaneous infect." "Requirements of such an animal model are simulation of humans infection, reproducible experimental disease and a similar degree of infection for all animals in a group." (See page 2639.)

Dr. Musser also makes statements concerning the reasonable predictability of animal tests of utility in humans is directed to M protein.

Although, Dr. Musser indicates that "animal tests such as these are reasonably predictive of utility in humans, it is unclear if this animal model correlates to and enables one of skill in the art to extrapolate to successful treatment in humans. (Indication of protection.)

However, Kehoe, cited, has indicated that group A streptococci express a wide array of antigenic extracellular products, which include the pyrogenic exotoxins. Kehoe indicates that "although antibodies to some of these products can modulate the course of particular diseases, only the M protein appears to be able to evoke effective protection."

Thus, Applicant cannot rely on the prior art "teachings" directed to a "known" streptococcal antigen, to enable one of ordinary skill in the art to use the protease as a vaccine in humans.

This ground of the enablement rejection asserts that Applicants have not provided sufficient evidence that the cysteine protease is effective in protecting against Group A streptococcal infections. The Examiner dismisses the Declaration of Dr. Musser which provides evidence in support of the asserted utility because it "does not follow the methodology set forth in the specification, but teaches s.c. inoculation followed by i.p. This method is not contemplated by the specification" (Office Action, p. 3, lines 17-19). This ground of rejection is improper for two reasons. First, Applicants point out that their specification is not limited to particular routes of administration. For example, at p. 8 lines 1-2, the specification states that "[t]he vaccine may be given by a number of different routes of administration. Preferably, the vaccine is given by parenteral administration."

Second, the Examiner has provided no evidence why one of skill in the art would expect a change in the route of inoculation to render the vaccine ineffective. Past experience

with another streptococcal antigen, the M protein, indicates that the particular route of inoculation employed is not critical. For example, Kehoe state that "[p]rotection studies in mice have examined a wide range of different vaccine formulations . . . and a variety of immunization routes . . . . All of these studies agree that systemic protection against group A streptococcal infection is very effective. . . ." (Kehoe, p. 799, first full paragraph).

The Examiner also dismisses the Declaration of Dr. Musser because the animal model used in the specification is allegedly not the same as that suggested in the specification. Applicants respectfully submit that this is irrelevant. In presenting evidence that a claimed invention is operable, there is no requirement that such evidence be derived from the same model system as that described in the specification. In fact, it seems that a demonstration that an invention works as claimed in an additional model system would be more convincing of utility than further data using the same model system previously described.

Next, the Examiner states that "the animal model does not typify or correlate to any 'infection' caused by S. pyogenes" (Office Action, p. 4). In support of this assertion, the Examiner mischaracterizes the teachings of Bunce *et al.* regarding the animal system used in Applicants' specification. Bunce *et al.* state that "[b]ecause previously reported animal models for staphylococcal infection have not closely simulated human cutaneous . . . infection, these models are more like animal test systems . . . ." (Bunce *et al.*, p. 2639, underlining indicates portion of the sentence not quoted by the Examiner). Thus, Bunce, *et al.* were referring to previously described model systems, not the one described in their paper. As for their own model system, Bunce *et al.* state that "[t]his hairless-mouse model of subcutaneous infection should be suitable both for comparing isogeneic strains of gram-positive cocci to examine factors necessary for the pathogenesis of cutaneous infections augmented by a foreign substance and for evaluating antibacterial agents" (p. 2640). The test as to whether an animal model is sufficient is whether those with skill in the art would find it reasonably predictive of utility in humans; the test does not have to be absolutely predictive, but rather one which would encourage moving to the next step of testing if the results are positive.

The Declaration of Dr. Musser states that the animal tests described in the Declaration are reasonably predictive of utility in humans. The Examiner, however, contradicts this statement of an expert in the field, asserting that "it is unclear if this animal model correlates to and enables one of skill in the art to extrapolate to successful treatment in humans. (induction of protection)" (Office Action, p. 4). The Examiner has provided no evidence as to why one of skill in the art would doubt the credibility of this statement. Therefore, she must accept Dr. Musser's statement that the animal tests described are reasonably predictive of utility in humans or provide an affidavit stating the facts upon which she bases her opinion to the contrary. 37 C.F.R. § 107(b).

The Examiner cites the Kehoe reference as evidence that one would not expect a cysteine protease vaccine to be effective against group A streptococcal infections. Kehoe state that "only the M protein appears able to evoke effective protection." Kehoe's statement may have been an accurate portrayal of the published art at the time the Kehoe paper was published, but it clearly cannot be read as precluding the possibility that some other streptococcal protein would be found effective as a vaccine in the future: Applicants have made this discovery, and have provided sufficient detail to enable one skilled in the art to make and use this discovery.

The experiment data set forth is inconclusion [*sic*] to allow a determination to be made regarding any effacacy [sic] of the cysteine protease as a "vaccine."

In one experiment, Dr. Musser indicates that only 2 of 9 cysteine protease animals survived at 120 hours, the "termination of the experiment."

The Declaration also indicates that the second experiment was "terminated" at 40 hours, approximately 2 days. (Page 3.) Fifty percent of vaccinated had died at this point.

However, the specification indicates that the time for 50% mortality for the PBS control mice is 26 hours, and 55 hours for cysteine protease treated mice. The death of 5 of the 11 animals appears to approximate the 50% mortality rate disclosed in the specification, suggesting that the cysteine protease is not effective to induce protective antibody.

The declaratory evidence is, therefore, insufficient to enable the scope of the claimed invention and enable the cysteine protease as a "vaccine" and in a method to prevent streptococcal infections in humans.

Therefore, the objection to the specification and the rejection of claims 1-17 under 35 U.S.C. § 112, first paragraph, is maintained.

Finally, the Examiner finds the experimental results inconclusive to establish that the cysteine protease is useful as a vaccine. Referring to the experiment described in ¶ 8 of Dr.

Musser's Declaration, the Examiner states that "the second experiment was 'terminated' at 40 hours" (Office Action, p. 5). However, the Declaration actually states that the mice were monitored "for a total of 157 hours after challenge," not 40 hours. This is six times longer than the time by which 50% of the control animals had died in the experiment described in Applicants' specification. In contrast, 12 of the 15 control animals in the same experiment described in ¶ 9 of the Musser Declaration died within 40 hours after challenge. Thus, the cysteine protease is clearly effective as a vaccine against group A streptococcal infection. Therefore, Applicants respectfully submit that this ground of rejection is improper and should be withdrawn.

The 35 U.S.C. §§ 102(b) and 103 Rejections over Bjorck *et al.*

(2) The rejection of claims 1-4 under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Björck et al is maintained.

Applicant contends that the "legal standard for anticipation is strict" and there "must be no difference between the claimed invention and the reference disclosure." Applicant contends that Björck et al describe an inhibitor of cysteine protease.

Björck et al indicate "we have synthesized peptide derivatives" mimicking the proposed proteinase binding centre of cystatin C. Several bacteria produce proteinases and the peptide was able to inhibit the activity of group A streptococci.

Claim 1 is broad and includes the terms "vaccine against." These terms are viewed as intended use and carry no patentable weight. Claim 2 includes the terms fragments or derivatives thereof, which the Björck et al peptide is viewed to be. Thus the disclosure of Björck et al reads on the claims as broadly drafted.

Applicants respectfully submit that the rejections of claims 1-4 as anticipated by Bjorck *et al.* are based upon a mischaracterization of the Bjorck *et al.* compound. Applicants' claims are directed to a vaccine that contains a conserved cysteine protease. The Examiner maintains her assertion that the Bjorck *et al.* peptide is a fragment or derivative of a cysteine protease even though Bjorck *et al.* clearly state that it is not. Bjorck *et al.* state that "[w]e have synthesized peptide derivatives mimicking the proposed proteinase-binding centre of cystatin C" (see the Abstract, emphasis added). The only connection that cystatin C has to cysteine proteases is that, as Bjorck *et al.* further state, "[c]ystatin C is a human cysteine protease inhibitor present in extracellular fluids" (see, the

Abstract, emphasis added). Thus, the Bjorck *et al.* compound is a fragment or derivative of cystatin C, which is not a cysteine protease.

Even more inexplicably, the rejection is maintained over Applicants' uncontroverted assertion that the Bjorck *et al.* compound has absolutely nothing in common with the compounds used in the Applicants' claimed vaccines and methods. It shares no part of its amino acid sequence with the cysteine protease compounds utilized in Applicants' claimed vaccines. This rejection is the antithesis of a proper anticipation rejection. Anticipation requires that there be no difference between the claimed invention and the reference disclosure. Here, there is no similarity between the claimed invention and the reference disclosure. Thus, this rejection is improper and should be withdrawn.

Nor does the Bjorck *et al.* reference render the invention of claims 1-4 *prima facie* obvious. A proper case of *prima facie* obviousness based on structural similarity requires that the compounds of the invention be identical or substantially identical to that of the prior art. *In re Best*, 195 USPQ 430, 433 (CCPA 1977). As stated above, the Bjorck *et al.* peptide has absolutely no similarity to the compounds used in Applicants' invention. The tripeptide described by Bjorck *et al.* is not found anywhere in the amino acid sequence of the cysteine protease used in Applicants' claimed compositions. Therefore, the Applicants respectfully submit that *prima facie* obviousness is not established.

(3) The rejection of claims 1-4, 6-17 under 35 U.S.C. § 103 as being unpatentable over Björck et al, in view of Kehoe et al and Fischetti et al is maintained.

The teachings of Björck et al which indicate that the peptide inhibits the activity of streptococcal proteinase is motivation to apply the cysteine protease in a method of immunizing.

As the prior art also indicates that the only known "protective" streptococcal antigen are the M antigens, it would have been obvious to include such antigen in the vaccine formulation.

The Examiner states that the obviousness rejection of claims 1-4 and 6-17 over Bjorck *et al.*, in view of Kehoe and Fischetti *et al.* "is maintained" (Office Action, p. 6, lines 1-3). Applicants respectfully submit that these claims were not previously rejected under this combination of references. Rather, these claims were rejected as obvious over the Bjorck *et*

al. reference alone. (It was claim 5 that was rejected as obvious over Bjorck *et al.* in view of Kehoe and Fischetti *et al*, see below.) Applicants respond accordingly.

As are the previously discussed prior art rejections, this rejection is based on the Examiner's mischaracterization of the Bjorck *et al.* peptide as a derivative of a cysteine protease, which it is not. Applicants' claims are directed to the use of a cysteine protease as a vaccine; the Bjorck *et al.* peptide is not a derivative of a cysteine protease. It is a derivative of cystatin C, which is not a cysteine protease. Since Bjorck *et al.* do not describe a cysteine protease derivative, the reference cannot suggest the use of a cysteine protease as a vaccine.

Furthermore, Bjorck *et al.* teach away from Applicants' invention. Bjorck *et al.* found that a cysteine protease inhibitor suppressed *S. pyogenes* growth *in vitro* and protected mice from lethal bacterial infection. In other words, according to the Bjorck *et al.* results, a decrease in cysteine protease activity is associated with a favorable pharmacological result. Yet the Examiner asserts that this teaching "is motivation" to give a patient more of this cysteine protease. This is the exact opposite of what the Bjorck *et al.* reference suggests to those of skill in the art.

The Examiner herself contradicts this ground of rejection by stating that "the prior art also indicates that the only known 'protective' streptococcal antigen are the M antigens . . . ." (Paper No 13, p. 6). If the prior art teaches that only the M proteins are protective, one of skill in the art would have no motivation to try a different streptococcal antigen such as the cysteine protease.

Turning now to the rejection of claim 5 as obvious over Bjorck *et al.* in view of Kehoe and Fischetti *et al.*, Applicants point out that this claim is directed to a vaccine that contains both a conserved cysteine protease and a streptococcal M protein antigen. A proper obviousness rejection requires that the cited prior art suggest the use of both of these peptides. According to the Examiner, Kehoe and Fischetti *et al.* both teach that M proteins are the only streptococcal antigens that are capable of evoking effective protection against group A streptococcal infections (Paper No. 10, p. 10, lines 9-16). Thus, Fischetti *et al.* and Kehoe clearly does not suggest the use of a cysteine protease in combination with an M

protein as a vaccine. This suggestion is not provided by Bjorck *et al.* because, as discussed above, Bjorck *et al.* do not describe a cysteine protease derivative. Therefore, this ground of rejection is improper and should be withdrawn.

The New Grounds of Rejection

The following are new grounds of rejection.

Claims 1, 2 are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is indefinite in the recitation of derivative thereof. It is unclear what Applicant intends by this term.

Further, "derivative thereof" is not defined in the specification. The specification also does not teach how to make and/or use said derivative thereof of the cysteine protease in a method of treatment.

Claims 1 and 2 stand newly rejected under 35 U.S.C. § 112, first and second paragraphs. However, specific grounds for the rejection are provided only for claim 2. Therefore, Applicants are unable to respond to this rejection as applied to claim 1. As for claim 2, to facilitate prosecution Applicants have removed the phrase "or derivatives thereof" to which the rejection is directed. Applicants reserve the right to later pursue claims directed to cysteine protease derivatives, in this or a subsequently filed application. In view of the amendment to claim 2, Applicants believe that this ground of rejection is obviated.

Claims 1-4 are rejected under 35 U.S.C. § 102(a/b) as being anticipated by Kapur et al or Tai et al or Hauser et al or Gerlach et al or Yonaha et al.

The claims are directed to a vaccine comprised of a cysteine protease.

Kapur et al (PNAS 90:7676-7680, 1993) disclose a composition of a S. pyogenes cysteine protease, which is conserved.

Tai et al (J. of Biological Chemistry 251:1955-1959, 1976) disclose a streptococcal proteinase. (Page 1956.)

Hauser et al (J. of Bact. 172:4536-4542, 1990) disclose a composition of exotoxin B. (See Materials and Methods, Toxin purification, page 4536.)

Yonaha et al (J. of Protein Chemistry 1:317-334, 1982) disclose streptococcal zymogen. (An extracellular proteinase.) (Attached is the sequence search.)

Kapur et al (Microbial Pathogenesis 15:327-346, 1993) disclose a S. pyogenes extracellular cysteine protease. (See page 341.)

Gerlach et al (Zbl. Bakt. Hyg., I. Abt. Orig 255:221-233, 1983) disclose the exotoxin B of S. pyogenes. (See the Summary, page 221.)

It is noted that the claims recite "vaccine" and "against Streptococcus pyogenes infection," however, these terms are viewed as intended use and carry no patentable weight.

Thus, the prior art disclosures anticipate that claimed.

The Examiner asserts that the terms "vaccine" and "against streptococcus pyogenes infection" in Applicants' claims are "viewed as intended use and carry no patentable weight" (Paper No. 13, p. 7, lines 8-10). However, the Examiner ignores the limitation that the vaccine compositions contain a physiologically acceptable vehicle in addition to the cysteine protease. As amended, claims 1-4 have an additional limitation: the conserved cysteine protease is present in an amount sufficient to confer immunity to group A streptococcal infection. None of the cited references describe either the conserved cysteine protease in combination with the physiologically acceptable vehicle, or a composition comprising the conserved cysteine protease in the specified amount.

These limitations as to a physiologically acceptable vehicle and the amount of the cysteine protease do carry patentable weight and cannot be read out of the claims to find anticipation. Nor are these limitations an obvious variant of the cysteine proteases described in the cited prior art. The CCPA has held that "absent a disclosure by [the cited prior art] of specific therapeutic or pharmaceutical uses for [a known compound], the addition of a pharmaceutical carrier to that compound and the determination of suitable dosage forms is not obvious." *In re Anthony*, 162 USPQ 594, 597 (CCPA 1969) (copy attached as Exhibit 4). The court stated that "[w]e do not think it is reasonable to assume, as the Patent Office seemingly has, that researchers would as a matter of course incorporate chemical compounds in specific amounts into pharmaceutically acceptable carriers and dosage unit forms unless they had some reasonably specific pharmaceutical use in mind." *Id.*

In the instant case, nearly every cited reference teaches exactly the opposite of a pharmaceutical use for the cysteine protease. The references teach that the streptococcal cysteine protease is harmful to humans and animals. Indeed, the very name of the compound, streptococcal pyrogenic exotoxin (SPEB) proclaims its toxic effects. Kapur *et al.* (*Proc. Nat'l. Acad. Sci. USA* 90: 7676-7680, 1993) state that "[s]treptococcal pyrogenic exotoxins (SPEs) share many biological properties, including fever induction and the ability to enhance susceptibility to endotoxic shock" and that "[s]ignificant evidence has accumulated

over several decades that SPEB is an important streptococcal virulence factor . . . ." (p. 7626). Hauser *et al.* (*J. Bact.* 172: 4536-4542, 1990) state that "[p]roperties of this family of toxins are T-cell mitogenicity, the ability to cause a scarlet fever-like rash, pyrogenicity, immunosuppression, and the ability to enhance susceptibility to exotoxin shock" (p. 4536, emphasis added). Kapur *et al.* (*Microbial Pathogenesis* 15: 327-346, 1993) state that the results described "suggest that the protease plays a role in bacterial dissemination, colonization, and invasion, and inhibition of wound healing" (p 327). With this knowledge, a clinician would not be motivated to administer more cysteine protease to a human or animal. Thus, there is no motivation in the cited prior art to incorporate the cysteine protease into pharmaceutically acceptable carriers in amounts sufficient to induce immunity against group A streptococci.

Only one of the cited references so much as mentions the use of a cysteine protease as a vaccine, and this reference sounds a note of caution. This reference (Kapur *et al.*, *Microbial Pathogenesis*, 1993) states that "[t]he observation that the cysteine protease is well conserved in naturally occurring clones responsible for most disease episodes and recovered from intercontinental sources decades apart, together with several lines of evidence that the protease is involved in the pathogenesis of *S. pyogenes* infections, may have significant implications for vaccine research" (p. 340). In view of the involvement of the cysteine protease in pathogenesis, one of skill in the art would be very cautious in administering the protease to a human or animal. However, given that other references, such as Kehoe teach away from the utility of using a cysteine protease as a vaccine ("only the M protein appears able to evoke effective protection") this precatory language in Kapur *et al.* can hardly be said to render the invention obvious in the absence of hindsight analysis.

Claims 5-17 are rejected under 35 U.S.C. § 103 as being unpatentable over Gerlach et al or Hauser, in view of Kehoe et al and Fischetti et al and Abe et al and Kapur et al.

Gerlach et al teach the exotoxin B of S. pyogenes.

Hauser et al also disclose the cysteine protease. However, the prior art does not use it in a method to immunize or with an M antigen.

Kehoe et al, cited, teach that the M proteins appear to be the only streptococcal antigens which are capable of evoking effective protection against group A streptococcal infections.

And Fischetti et al, cited, similarly teach that "type-specific antibodies to the M molecules are necessary to protect [a] host once streptococcal group A infection has initiated." (See page 1490.)

Kapur et al, cited, teach streptococcal cysteine protease and that patients with fatal streptococcal infection have lower antibody levels to SPEB than individuals with less severe infections. (See page 7676.) Kapur et al suggest that extracellular cysteine protease made by human microbial pathogens are important in host-parasite interactions. Kapur et al indicate that SPEB might have an important role in streptococcal pathogenesis and suggest potentially useful approaches for therapeutic intervention in the molecular pathogenesis pathway. (See page 7679, last paragraph.)

Gerlach et al further teaches that erythrogenic toxins are believed to be responsible for a wide spectrum of biological activities, such as skin reactions, toxicity; mitogenicity and relationship has been suggested between B toxin production and nephriogenicity of streptococcal strains, as high antiproteinase antibody titer is found in patients suffering from glomerulonephritis. (See page 230.)

Abe et al (Journal of Immunology 146:3747-50, 1991) teach that streptococcal exotoxins have been implicated in the pathogenesis of toxic shock syndrome and scarlet fever. Abe et al suggest that SPEB is a "superantigen" which may mediate some of the systemic syndromes associated with streptococcal infections.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the exotoxin B in a method to immunize, with the expectation of inducing antibodies which would neutralize the exotoxin B. Further, it would have been obvious to comprise the (exotoxin B) cysteine protease, with another known streptococcal antigen, for the expected benefits of inducing antibody to the only known streptococcal antigens which protect against experimental streptococcal infections.

A proper case of *prima facie* obviousness requires that the prior art provide both of the following: 1) a suggestion to practice the claimed invention, and 2) a reasonable expectation of success. Neither element of this test is satisfied by the cited references.

Claim 5 is directed to a vaccine composition that comprises a streptococcal M protein antigen, a conserved cysteine protease in an amount sufficient to induce immunity to group A streptococci, and a physiologically acceptable non-toxic vehicle. Claims 6-17 are directed to a method of immunizing mammals against *Streptococcus pyogenes* infection by administering a vaccine composition that comprises a conserved cysteine protease and a physiologically acceptable non-toxic vehicle. No cited reference suggests that the streptococcal cysteine protease is useful as a vaccine. In fact, the cited references teach away from Applicants' invention.

As described in the Abe *et al.* reference, SPEB is a "superantigen," which is defined as a molecule that is able to activate many T cells. Unlike typical antigens, which are processed by antigen-presenting cells and presented to helper T cells on specific MHC molecules superantigens are able to bind directly to both the T cell receptor and the MHC V_{β} region of the MHC molecule. Thus, superantigens bypass the normal process by which only T cells specific to an antigen are activated. A superantigen can activate up to 20% or more of the T cells in an organism; this is several orders of magnitude more than are normally

activated in response to an antigen. This T cell activation directly causes massive cytokine production, which in turn results in serious adverse clinical effects.

These adverse clinical effects are well-documented in the cited references. Abe *et al.* state that "[w]e speculate that the capacity of Group A streptococcus to produce a variety of superantigens (SPEA, SPEB, and the M protein) each of which induces the activation of T cells bearing different T cell specificities may result in a wide spectrum of human diseases" (Abe *et al.*, p. 3750) (emphasis added). Gerlach *et al.* state, as acknowledged by the Examiner, that toxins such as SPEB are "believed to be responsible for a wide spectrum of biological activities: skin reaction, toxicity, mitogenicity, reduction of the amount of leukocytes, change in permeability of the blood-brain-barrier, influence on the immune response and induction of interferon" (Gerlach *et al.*, p. 230). Hauser *et al.* also describe the adverse effects of SPEB, as discussed above. Similarly, Kapur *et al.* state that SPEB might have an important role in streptococcal pathogenesis (Kapur *et al.*, *Proc. Nat'l. Acad. Sci. USA* at 7679). Kapur *et al.* also note that "[p]urified SPEB injected into rabbits causes myocardial necrosis" (p. 7676).

The Examiner refers to the statement of Kapur *et al.* that patients with fatal streptococcal infection have lower antibody levels to SPEB than individuals with less severe infections. This result is not surprising in view of the above-described effects of SPEB and other superantigens on the immune system. Administration of superantigens such as SPEB is known to result in profound immunodeficiency that is probably due to the high levels of cytokine produced in response to the superantigens (*see, e.g.*, Abbas *et al.*, *Cellular and Molecular Immunology*, W.B. Saunders Co., Philadelphia, 1994, p. 323) (copy attached as Exhibit 5). This immunosuppressive effect is also noted by Hauser *et al.* ("[p]roperties characteristic of this family of toxins are . . . immunosuppression," p. 4536). The immunosuppressive effect of SPEB, not the presence of too little SPEB to stimulate antibody production, is likely responsible for the lower antibody levels in patients with fatal streptococcal infection.

Thus, prior to Applicants' invention, the expected effect of inoculating a mammal with the cysteine protease is not the induction of antibody. Rather, the expected effect was a immunosuppression and a wide variety of adverse and potentially fatal reactions.

Furthermore, Kehoe and Fischetti *et al.* explicitly teach away from Applicants' invention. These references both teach that the streptococcal M protein is the only streptococcal antigen that is able to evoke effective protection against streptococcal group A infections. Kehoe states that:

> "[t]he ability of M protein to elicit highly protective antibody was first suggested in 1919 by Lancefield's mouse protection experiments and has been confirmed repeatedly by seven decades of subsequent research and clinical observations. It is, therefore, not surprising that most attempts to develop group A streptococcal vaccines have focused almost exclusively on this highly protective antigen." (p. 798-799, bridging paragraph)

In seven decades of research into vaccines against group A streptococci, no persons other than the present Applicants have suggested the use of a streptococcal cysteine protease as a vaccine. It is difficult to imagine a more clear-cut case of non-obviousness.

In summary, the Applicants' invention is neither anticipated nor rendered obvious by the cited references. The cited references do not describe a composition comprising a pharmaceutically acceptable carrier and a conserved cysteine protease in an amount sufficient to protect against streptococcal infection. Nor do the cited references provide motivation to make such a composition, because the references teach that the cysteine protease causes harmful effects, not beneficial effects. Likewise, the cited references do not render obvious Applicants' claimed methods of immunizing with the cysteine protease to protect against streptococcal infection. Instead, the references suggest that inoculating with a streptococcal cysteine protease will cause immunosuppression and other harm to the patient. Therefore, Applicants respectfully submit that these grounds of rejection are improper and should be withdrawn.

CONCLUSION

In view of the above amendment and remarks, it is submitted that this application is now ready for allowance. Early notice to that effect is solicited. If in the opinion of the

Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned at (415) 926-6202.

Respectfully submitted,

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